What is claimed is:

1. A method for identifying a ligand for a hydrophobic protein, the method comprising
   (a) selecting a ligand molecule by affinity selection by exposing a hydrophobic target protein bound by an amphiphile to a multiplicity of molecules to promote the formation of at least one complex between the hydrophobic target protein and the ligand molecule,
   (b) separating the complex from the unbound molecules, and
   (c) identifying the ligand molecule.

2. The method of claim 1, wherein exposure of the hydrophobic target protein to a multiplicity of molecules occurs under homogeneous solution phase conditions.

3. The method of claim 1, wherein exposure of the hydrophobic target protein to a multiplicity of molecules occurs under heterogeneous solution phase conditions.

4. The method of claim 1, wherein selection of the ligand molecule is done using multi-dimensional chromatography.

5. The method of claim 1, wherein the hydrophobic target protein is selected from the group consisting of:
   (a) of a membrane protein,
   (b) an integral membrane protein,
   (c) a transmembrane protein,
   (d) a monotopic membrane protein,
   (e) a polytopic membrane protein,
   (f) a pump protein,
   (g) a channel protein,

(h) a receptor kinase protein,
(i) a G protein-coupled receptor protein,
(j) a membrane-associated enzyme, and
(k) a transporter protein.

6. The method of claim 1, wherein the multiplicity of molecules is a mass-coded library of molecules.

7. The method of claim 1, wherein the multiplicity of molecules is a library of molecules that is not mass-coded.

8. The method of claim 1, wherein the amphiphile is selected from the group consisting of:
(a) a polar lipid,
(b) an amphiphilic macromolecular polymer,
(c) a surfactant or detergent, and
(d) an amphiphilic polypeptide.

9. The method of claim 1, wherein ligand molecule identification is done by mass spectral analysis.

10. The method of claim 1, wherein the ligand molecule is deconvoluted by mass spectral analysis.

11. The method of claim 1, wherein separation of the complex from the unbound molecules is accomplished with solid phase chromatography media.

12. The method according to claim 1, wherein the hydrophobic target protein comprises
(a) at least one transmembrane domain sequence,
(b) at least two tag sequences useful for affinity selection, and
(c) a hydrophobic protein (HP) sequence.

13. The method according to claim 12, wherein the hydrophobic protein sequence is selected from the group consisting of
(a) of a membrane protein,

(b) an integral membrane protein,
(c) a transmembrane protein,
(d) a monotopic membrane protein,
(e) a polytopic membrane protein,
(f) a pump protein,
(g) a channel protein,
(h) a receptor kinase protein,
(i) a G protein-coupled receptor protein,
(j) a membrane-associated enzyme, and
(k) a transporter protein.

14. The method according to claim 12, wherein the tag sequences comprise epitope tag sequences selected from the group consisting of
(a) a FLAG tag (NH2-DYKDDDDK-COOH) (SEQ ID NO:29),
(b) an EE tag (NH2-EEEEYMPME-COOH) (SEQ ID NO:30),
(c) a hemagglutinin tag (NH2-YPYDVPDYA-COOH) (SEQ ID NO:31),
(d) a myc tag (NH2-KHKLEQLRNSGA-COOH) (SEQ ID NO:32), and
(e) an HSV tag (NH2-QPELAPEDPED-COOH) (SEQ ID NO:33).

15. The method according to claim 12, wherein the hydrophobic target protein comprises a sequence with an amino terminus to carboxy terminus order selected from the group consisting of
(a) Tag1-Tag2-HP,
(b) Tag1-HP-Tag2, and
(c) HP-Tag1-Tag2.

16. The method according to claim 15, wherein the hydrophobic target protein is selected from the group consisting of
(a) Myc tag-EE tag-Human m2 mAChR (SEQ ID NO:7),
(b) Flag tag-Human Beta 2 Adrenergic Receptor-EE tag (SEQ ID NO:8),

(c) Human Neurokinin 3 Receptor-HSV tag-Myc tag (SEQ ID NO:9),

(d) Flag tag-Human m1 mAChR-EE tag (SEQ ID NO:10), and

(e) Rat m3 mAChR-HSV tag-OctaHis tag (SEQ ID NO:11).

17. The method according to claim 15, wherein the hydrophobic target protein further comprises a heterologous signal sequence (SS) at the amino terminus.

18. The method according to claim 17, wherein the heterologous signal sequence is selected from the group consisting of

(a) the Mellitin signal sequence of NH_2-KFLVNVALVFMVVYISYIYA-COOH (SEQ ID NO:12),

(b) the GP signal sequence of NH_2-VRTAVLILLLVRFSEP-COOH (SEQ ID NO:13),

(c) the Hemagglutinin signal sequence of NH_2-KTIIALSYIFCLVFA-COOH (SEQ ID NO:14),

(d) the rhodopsin tag 1 signal sequence of NH_2-MNGTEGPNFYVPFSNKTGVVRSPFEAPQYYLAEP-COOH (SEQ ID NO:15), and

(e) the rhodopsin tag ID4 signal sequence of NH_2-GKNPLGVRKTETSQVAPA-COOH (SEQ ID NO:16).

19. The method according to claim 18, wherein the tag sequences further comprise a hexahistidine sequence (SEQ ID NO:17) and a decahistidine sequence (SEQ ID NO:18).

20. The method according to claim 19, wherein the hydrophobic target protein is selected from the group consisting of

(a) GP67 SS-Myc tag-EE tag-Human m2 mAChR (SEQ ID NO:19),

(b) Mellitin SS-Flag tag-Human Beta 2 Adrenergic Receptor-EE tag(SEQ ID NO:20),

(c) Hemagglutinin SS-Human Neurokinin 3 Receptor-HSV tag-Myc tag (SEQ ID NO:21),

(d) Mellitin SS-Flag tag-Human m1 mAChR-EE tag (SEQ ID NO:22), and

(e) Hemagglutinin SS-Rat m3 mAChR-HSV tag-OctaHis tag (SEQ ID NO:23).

21. A method of isolating a hydrophobic protein, the method comprising

(a) purifying the hydrophobic protein by sucrose gradient ultracentrifugation,

(b) purifying the hydrophobic protein by antibody affinity purification, and

(c) purifying the hydrophobic protein by immobilized metal affinity chromatography.

22. The method of claim 21, wherein the hydrophobic protein comprises

(a) at least one transmembrane domain sequence,

(b) at least two tag sequences useful for affinity selection, and

(c) a hydrophobic protein (HP) sequence.

23. The method according to claim 22, wherein the hydrophobic protein sequence is selected from the group consisting of

(a) a membrane protein,

(b) an integral membrane protein,

(c) a transmembrane protein,

(d) a monotopic membrane protein,

(e) a polytopic membrane protein,

(f) a pump protein,

(g) a channel protein,

(h) a receptor kinase protein,

(i) a G protein-coupled receptor protein,

(j) a membrane-associated enzyme, and

(k) a transporter protein.

24. The method according to claim 22, wherein the tag sequences comprise epitope tag sequences selected from the group consisting of
(a) a FLAG tag (NH2-DYKDDDDK-COOH) (SEQ ID NO:29),
(b) an EE tag (NH2-EEEEYMPME-COOH) (SEQ ID NO:30),
(c) a hemagglutinin tag (NH2-YPYDVPDYA-COOH) (SEQ ID NO:31),
(d) a myc tag (NH2-KHKLEQLRNSGA-COOH) (SEQ ID NO:32), and
(e) an HSV tag (NH2-QPELAPEDPED-COOH) (SEQ ID NO:33).

25. The method according to claim 22, wherein the hydrophobic protein comprises a sequence with an amino terminus to carboxy terminus order selected from the group consisting of
(a) Tag1-Tag2-HP,
(b) Tag1-HP-Tag2, and
(c) HP-Tag1-Tag2.

26. The method according to claim 22, wherein the hydrophobic protein is selected from the group consisting of
(a) Myc tag-EE tag-Human m2 mAChR (SEQ ID NO:7),
(b) Flag tag-Human Beta 2 Adrenergic Receptor-EE tag (SEQ ID NO:8),
(c) Human Neurokinin 3 Receptor-HSV tag-Myc tag (SEQ ID NO:9),
(d) Flag tag-Human m1 mAChR-EE tag (SEQ ID NO:10), and
(e) Rat m3 mAChR-HSV tag-OctaHis tag (SEQ ID NO:11).

27. The method according to claim 22, wherein the hydrophobic protein further comprises a heterologous signal sequence (SS) at the amino terminus.

28. The method according to claim 27, wherein the heterologous signal sequence is selected from the group consisting of

(a) the Mellitin signal sequence of NH_2-KFLVNVALVFMVVYISYIYA-COOH (SEQ ID NO:12),

(b) the GP signal sequence of NH_2-VRTAVLILLLVRFSEP-COOH (SEQ ID NO:13),

(c) the Hemagglutinin signal sequence of NH_2-KTIIALSYIFCLVFA-COOH (SEQ ID NO:14),

(d) the rhodopsin tag 1 signal sequence of NH_2-MNGTEGPNFYVPFSNKTGVVRSPFEAPQYYLAEP-COOH (SEQ ID NO:15), and

(e) the rhodopsin tag ID4 signal sequence of NH2-GKNPLGVRKTETSQVAPA-COOH (SEQ ID NO:16).

29. The method according to claim 14, wherein the tag sequences further comprise a hexahistidine sequence (SEQ ID NO:17) and a decahistidine sequence (SEQ ID NO:18).

30. The method according to claim 29, wherein the hydrophobic target protein is selected from the group consisting of

(a) GP67 SS-Myc tag-EE tag-Human m2 mAChR (SEQ ID NO:19),

(b) Mellitin SS-Flag tag-Human Beta 2 Adrenergic Receptor-EE tag(SEQ ID NO:20),

(c) Hemagglutinin SS-Human Neurokinin 3 Receptor-HSV tag-Myc tag (SEQ ID NO:21),

(d) Mellitin SS-Flag tag-Human m1 mAChR-EE tag (SEQ ID NO:22), and

(e) Hemagglutinin SS-Rat m3 mAChR-HSV tag-OctaHis tag (SEQ ID NO:23).

31. An isolated nucleic acid molecule suitable for hydrophobic protein expression, comprising

(a) a vector polynucleotide sequence for protein expression in a eukaryotic cell, and

(b) a polynucleotide sequence encoding an engineered hydrophobic protein comprising the following elements

(i) an N-terminal methionine residue,

(ii) a heterologous signal sequence (SS),

(iii) at least one transmembrane domain sequence,

(iv) at least two tag sequences useful for affinity selection, and

(v) a hydrophobic protein (HP) sequence.

32. The isolated nucleic acid molecule of claim 32, wherein the N-terminal methionine sequence and the heterologous signal sequence are selected from the group consisting of

(a) MKFLVNVALVFMVVYISYIYA (SEQ ID NO:24),

(b) MVRTAVLILLLVRFSEP (SEQ ID NO:25),

(c) MKTIIALSYIFCLVFA (SEQ ID NO:26)

(d) MMNGTEGPNFYVPFSNKTGVVRSPFEAPQYYLAEP-COOH (SEQ ID NO:27) and

(e) MGKNPLGVRKTETSQVAPA-COOH (SEQ ID NO:28).

33. The isolated nucleic acid molecule of claim 33, wherein the tag sequences comprise epitope tag sequences selected from the group consisting of

(a) a FLAG tag (NH2-DYKDDDDK-COOH) (SEQ ID NO:1),

(b) an EE tag (NH2-EEEEYMPME-COOH) (SEQ ID NO:2),

(c) a hemagglutinin tag (NH2-YPYDVPDYA-COOH) (SEQ ID NO:3),

(d) a myc tag (NH2-KHKLEQLRNSGA-COOH) (SEQ ID NO:4), and

(e) an HSV tag (NH2-QPELAPEDPED-COOH) (SEQ ID NO:5).

34. The isolated nucleic acid molecule of claim 33, wherein the elements of the engineered hydrophobic protein are arrayed from an amino to carboxy terminus order selected from the group consisting of

(a) SS-Tag1-Tag2-HP,
(b) SS-Tag1-HP-Tag2, and
(c) SS-HP-Tag1-Tag2.

35. The isolated nucleic acid molecule of claim 34, wherein the tag sequences further comprise a hexahistidine sequence (SEQ ID NO:17) and a decahistidine sequence (SEQ ID NO:18).

36. The isolated nucleic acid molecule of claim 35, wherein the engineered hydrophobic protein is selected from the group consisting of
(a) GP67-Myc-EE-Human m2 mAChR (SEQ ID NO:19),
(b) Mellitin-Flag Tag-Human m1 mAChR-EE (SEQ ID NO:20), and

37. A method for identifying a ligand for a hydrophobic protein, the method comprising
(a) selecting a hydrophobic target protein from the group consisting of
(i) of a membrane protein,
(ii) an integral membrane protein,
(iii) a transmembrane protein,
(iv) a monotopic membrane protein,
(v) a polytopic membrane protein,
(vi) a pump protein,
(vii) a channel protein,
(viii) a receptor kinase protein,
(ix) a G protein-coupled receptor protein,
(x) a membrane-associated enzyme, and
(xi) a transporter protein,
(xii) wherein the hydrophobic protein is bound by amphiphile;
(b) selecting an amphiphile to bind the hydrophobic protein from the group consisting of:
(i) a polar lipid,
(ii) an amphiphilic macromolecular polymer,
(iii) a surfactant or detergent, and

(iv) an amphiphilic polypeptide;

(c) selecting a ligand molecule using multi-dimensional chromatography by affinity selection by exposing under homogenous solution phase conditions the hydrophobic target protein bound by an amphiphile to a multiplicity of molecules from a mass-coded library to promote the formation of at least one complex between the hydrophobic target protein and the ligand molecule;

(d) separating the complex from the unbound molecules; and

(e) identifying the ligand molecule by mass spectral analysis.

38. A method for identifying a ligand for a hydrophobic protein, the method comprising

(a) selecting a hydrophobic target protein from the group consisting of

(i) of a membrane protein,

(ii) an integral membrane protein,

(iii) a transmembrane protein,

(iv) a monotopic membrane protein,

(v) a polytopic membrane protein,

(vi) a pump protein,

(vii) a channel protein,

(viii) a receptor kinase protein,

(ix) a G protein-coupled receptor protein,

(x) a membrane-associated enzyme, and

(xi) a transporter protein,

(xii) wherein the hydrophobic protein is bound by amphiphile;

(b) selecting an amphiphile to bind the hydrophobic protein from the group consisting of:

(i) a polar lipid,

(ii) an amphiphilic macromolecular polymer,

(iii) a surfactant or detergent, and

(iv) an amphiphilic polypeptide;

(c) selecting a ligand molecule using multi-dimensional chromatography by affinity selection by exposing under heterogeneous solution phase conditions a hydrophobic target protein bound by an amphiphile to a multiplicity of molecules from a library that is not mass-coded to promote the formation of at least one complex between the hydrophobic target protein and the ligand molecule;

(d) separating the complex from the unbound molecules,;and

(e) identifying the ligand molecule by mass spectral analysis.

39. A method of isolating a hydrophobic protein, the method comprising

(a) selecting a hydrophobic protein comprising

(i) at least one transmembrane domain sequence,

(ii) at least two tag sequences useful for affinity selection,selected from the group consisting of:

(1) a FLAG tag (NH2-DYKDDDDK-COOH) (SEQ ID NO:29),

(2) an EE tag (NH2-EEEEYMPME-COOH) (SEQ ID NO:30),

(3) a hemagglutinin tag (NH2-YPYDVPDYA-COOH) (SEQ ID NO:31),

(4) a myc tag (NH2-KHKLEQLRNSGA-COOH) (SEQ ID NO:32), and

(5) an HSV tag (NH2-QPELAPEDPED-COOH) (SEQ ID NO:33);

(iii) a hydrophobic protein (HP) sequence selected from the group consisting of:

(1) a membrane protein,

(2) an integral membrane protein,

(3) a transmembrane protein,

(4) a monotopic membrane protein,
(5) a polytopic membrane protein,
(6) a pump protein,
(7) a channel protein,
(8) a receptor kinase protein,
(9) a G protein-coupled receptor protein,
(10) a membrane-associated enzyme, and
(11) a transporter protein;

(b) purifying the hydrophobic protein by sucrose gradient ultracentrifugation;

(c) purifying the hydrophobic protein by antibody affinity purification;and

(d) purifying the hydrophobic protein by immobilized metal affinity chromatography.

40. An isolated nucleic acid molecule suitable for hydrophobic protein expression, comprising

(a) a vector polynucleotide sequence for protein expression in a eukaryotic cell; and

(b) a polynucleotide sequence encoding an engineered hydrophobic protein comprising the following elements

(i) an N-terminal methionine residue,

(ii) a heterologous signal sequence (SS), wherein the N-terminal methionine sequence and the heterologous signal sequence are selected from the group consisting of

(1) MKFLVNVALVFMVVYISYIYA (SEQ ID NO:24),

(2) MVRTAVLILLLVRFSEP (SEQ ID NO:25),

(3) MKTIIALSYIFCLVFA (SEQ ID NO:26)

(4) MMNGTEGPNFYVPFSNKTGVVRSPFEAPQYYL AEP-COOH (SEQ ID NO:27) and

(5) MGKNPLGVRKTETSQVAPA-COOH (SEQ ID NO:28),

(iii) at least one transmembrane domain sequence;

(iv) at least two tag sequences useful for affinity selection selected from the group consisting of

(1) a FLAG tag (NH2-DYKDDDDK-COOH) (SEQ ID NO:1),

(2) an EE tag (NH2-EEEEYMPME-COOH) (SEQ ID NO:2),

(3) a hemagglutinin tag (NH2-YPYDVPDYA-COOH) (SEQ ID NO:3),

(4) a myc tag (NH2-KHKLEQLRNSGA-COOH) (SEQ ID NO:4), and

(5) an HSV tag (NH2-QPELAPEDPED-COOH) (SEQ ID NO:5), and

(v) a hydrophobic protein (HP) sequence selected from the group consisting of:

(1) a membrane protein,

(2) an integral membrane protein,

(3) a transmembrane protein,

(4) a monotopic membrane protein,

(5) a polytopic membrane protein,

(6) a pump protein,

(7) a channel protein,

(8) a receptor kinase protein,

(9) a G protein-coupled receptor protein,

(10) a membrane-associated enzyme, and

(11) a transporter protein.